# Synopsis

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**Registration no.:** 27/Ph.D./DPSRU/2018

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**Title of Thesis-** "Curcumin loaded Invasomal Gel for the treatment of Psoriasis: Formulation, Characterization and *In vivo* studies"

## 1. Introduction

Psoriasis is a recurrent, life-threatening anti-inflammatory disease that affects 1-3 % of the global population [1]. It is an autoimmune illness distinguished by hyperplasia of skin cells, or fast skin cell development, resulting in abnormal irritating scales and skin patches. It most usually affects the fingers and toes, palms, soles, scalp, elbows, knees, genital regions, umbilicus, sacrum, and gluteus maximus [2]. It has significant physical, emotional, psychological, and social influence on an individual, resulting in increased stress, low self-esteem, and poor interpersonal relationships [3].

Curcumin is a well-known bright yellow coloured polyphenol which is produced by the plants of curcuma long class belonging to family *Zingiberaceae*. It is being used in the therapeutic field since ancient times for the treatment of several diseases [1]. It effectively adheres to a range of biomolecules and inhibits the action of inflammatory enzymes, as well as regulates the production of numerous proteins, chemical messengers and adhesion molecules by modifying the functions of various transcription factors. It has significant clinical utility via approaches that target diverse molecular domains, making it a multifunctional chemical moiety with numerous therapeutic benefits such as antifungal, antimutagenic, anticarcinogenic, antibacterial, antiviral and antiulcer [2]. Antipsoriatic potential of curcumin has been reported using imiquimod induced psoriatic plaque model. As a selective phosphorylase kinase inhibitor, it actively suppresses mitogen activated protein kinase, nuclear factor kappa B (NF-kB) and cytokines. By inactivating

NF-kB, it reduces the expression of many proinflammatory cytokines. It inhibits the phosphorylation and nuclear translocation of transcriptional signal transducers and activators (STATs) [4]. Thereby blocking the cytokines, NF-kB, and STAT3 activation, which are the contributors to inflammation and keratinocyte proliferation in psoriasis [5,6] . Use of curcumin through oral and parenteral route is restricted due to poor water solubility, degradation in the gastric tract, hepatic and intestinal metabolism, reduced absorption by the tissues and higher rate of systemic clearance which leads to poor bioavailability. These drawbacks associated with the oral and parenteral routes can be bypassed by delivering curcumin through the transdermal route. However, poor skin permeability, limited water solubility and excellent barrier properties of the stratum corneum pose serious challenges to its transdermal distribution and effectiveness [2].

Invasomes are flexible phospholipid-based nanoscale vesicular systems composed of phosphatidylcholine, ethanol, terpenes or a blend of terpenes with considerably more percutaneous permeation than standard liposomes [5,6]. Terpenes are potent permeation boosters that readily affects the packing of stratum corneum, disrupt its lipid structure, react with intracellular proteins, and significantly augments the stratum corneum drug partitioning [7,8]. Ethanol and terpenes present in the invasomes extend a synergistic impact which promotes invasomal vesicle penetration through the skin [9,10]. Invasomes offer a number of advantages such as non-invasive drug delivery, improved drug permeation across the skin, delivery of both lipophilic and hydrophilic drugs and increased patient compliance as the drug is available in semisolid form that is a gel or cream. The research focused on promoting the topical administration of curcumin through nano sized invasomal vesicles in order to generate a topical formulation with enhanced curcumin transport across the skin for improved therapeutic activity in psoriasis [11,12]

**2. Research Rationale:**

Psoriasis is a recurrent, life-threatening anti-inflammatory disease that affects 1-3 % of the global population. It is an autoimmune illness distinguished by hyperplasia of skin cells, or fast skin cell development, resulting in abnormal irritating scales and skin patches. It most usually affects the fingers and

toes, palms, soles, scalp, elbows, knees, genital regions, umbilicus, sacrum, and gluteus maximus. It has significant physical, emotional, psychological, and social influence on an individual, resulting in increased stress, low self-esteem, and poor interpersonal relationships. Even though psoriasis is not life threatening, reported research suggested an increased risk of cardiovascular disease, diabetes, and cancer among other morbidities. The major interventions of psoriasis therapy include phototherapy and systemic oral/topical treatments. Unfortunately, phototherapy and oral systemic drugs such as methotrexate, cyclosporine etc. do not show optimum therapeutic outcomes due to the shortcomings associated with them like low efficacy and safety issues including possible tissue toxicity and carcinogenicity. Hence, novel strategy is required which would offer amelioration of disease without presenting excessive load of side effects. Antipsoriatic potential of curcumin has been reported using imiquimod induced psoriatic plaque model Use of curcumin through oral and parenteral route is restricted due to poor water solubility, degradation in the gastric tract, hepatic and intestinal metabolism, reduced absorption by the tissues and higher rate of systemic clearance which leads to poor bioavailability. These drawbacks associated with the oral and parenteral routes can be by passed by delivering curcumin through the transdermal route. However, poor skin permeability, limited water solubility and excellent barrier properties of the stratum corneum pose serious challenges to its transdermal distribution and effectiveness. Invasomes are flexible phospholipid-based nanoscale vesicular systems composed of phosphatidylcholine, ethanol, terpenes or a blend of terpenes with considerably more percutaneous permeation than standard liposomes which can offer a number of advantages such as non-invasive drug delivery, improved drug permeation across the skin and delivery of both lipophilic and hydrophilic drugs.

**3. Objectives:**

The precise objectives of the present research work are:

1. Design, development and evaluation of curcumin invasomes for enhanced transdermal delivery **(Completed)**

2. To study the penetration enhancing effect of different terpenes present in the invasomes **(Completed)**
3. Formulation and evaluation of topical invasomal gel of curcumin for effective management of plaque psoriasis **(Completed)**

**4. Methodology**:

Curcumin loaded invasomes were prepared using three different terpenes viz Citral, Nerolidol and Eucalyptol through mechanical dispersion technique. The formulations were divided into three different batches depending on the concentration of terpenes that is 0.5%, 1% and 1.5%.

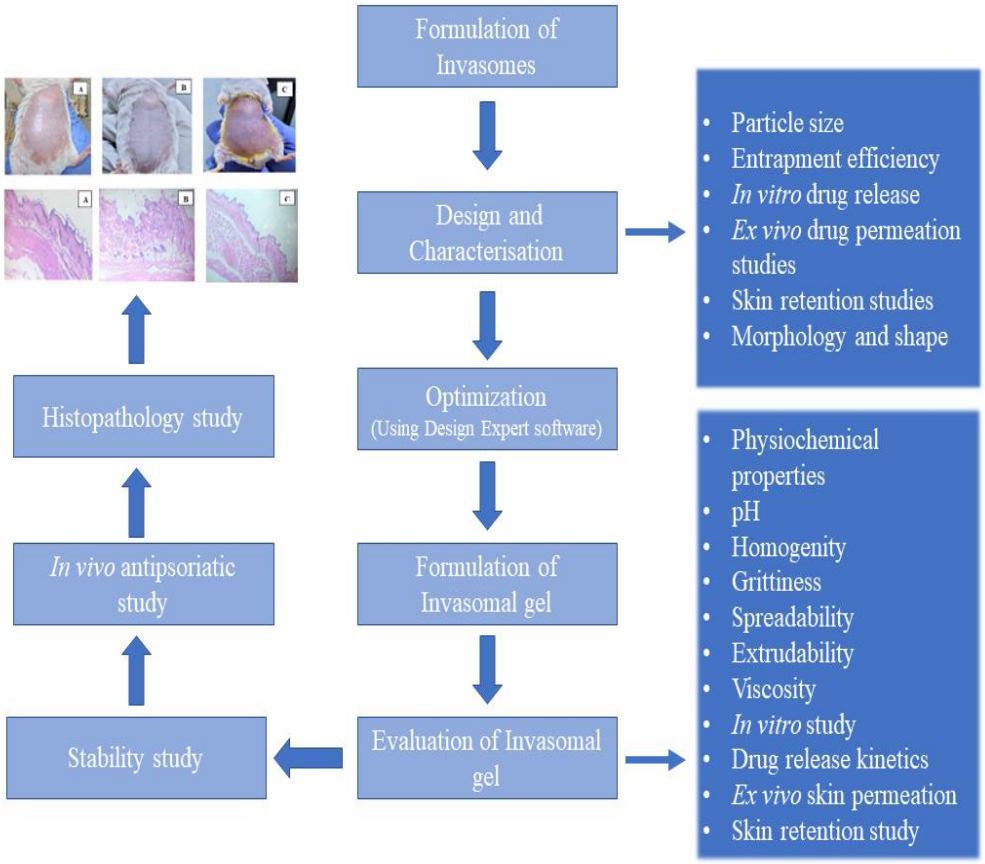


*Fig 1. Schematic representation of Methodology*

**5. Results:**

**Objective I:** ***Design, development and evaluation of curcumin invasomes for enhanced transdermal delivery :*** Curcumin loaded invasomes were prepared using three different terpenes viz Citral, Nerolidol and Eucalyptol through mechanical dispersion technique. The formulations were divided into three different batches depending on the concentration of terpenes that is 0.5%, 1% and 1.5%. The prepared invasomal formulations were characterised on the basis of vesicle size, entrapment efficiency, *in vitro* drug release and *ex vivo* skin permeation. Curcumin entrapment efficiency in various invasomal formulations was found to be ranging from 78.21± 0.50% to 85.84± 0.56% and the vesicle size ranged from 246.33±3.79 to 475.76±2.08 nm.

*In vitro* drug release study affirmed that all the formulations showed a higher curcumin release than the simple drug solution. After 24 hrs, the invasomal formulation made with citral (0.5%, 1% and 1.5%) showed the maximum cumulative release of 4599.21±2.15, 4651.40± 2.74 and 4973.87±3.91µg/cm$^2$ whereas the cumulative release of curcumin from simple drug solution was found to be 1894.56±3.30 µg/cm$^2$. *Ex vivo* skin permeation studies were performed using pig ear skin for 24 hours. The cumulative permeation of the formulated curcumin invasomes ranged from 3589.00±1.70 to 4335.11± 1.19 µg/cm$^2$.

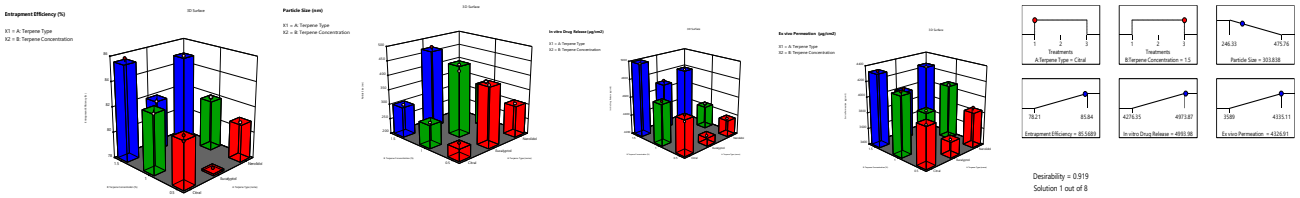


*Fig 2. 3D plots of factorial Design and Optimization of formulation*

A $3^{1}.3^{1}$ factorial design was utilised to determine and ameliorate the influence of terpene type and its concentration on the different attributes of formulated curcumin invasomes. Two factors were utilised by the design, both at three levels i.e., $X_1$: Terpene Type and $X_2$: Terpene concentration. Factorial Analysis demonstrated that the predicted $R^2$ values correspond well with the adjusted $R^2$ values for all of the study responses. All responses exhibited sufficient accuracy (higher than 4), indicating that the model can be utilised for investigating the design space. Analysis of variance reveal that $X_1$ and $X_2$ (both the independent

variables) had a substantial impact on the entrapment efficiency, vesicle size, drug release and drug permeation ($p< 0.05$ and $p<0.05$, respectively) (*Fig 2*). Numerical and graphical analysis was performed on the optimized variables in order to obtain Curcumin-loaded invasomes with the highest entrapment efficiency, smallest particle size, highest cumulative release and highest amount of drug permeation after 24 hours. Formulation C3 formulated with citral at a concentration of 1.5%, yielding a desirability of 0.919 was chosen for further investigation.

The optimized invasomal formulation showed an average particle size of 282.0±1.53 nm with polydispersity index (PDI) of 0.354 ±0.01 indicating narrow particle size distribution. FTIR spectra and DSC thermograms were also studied for the optimized formulation (*Fig 3*)

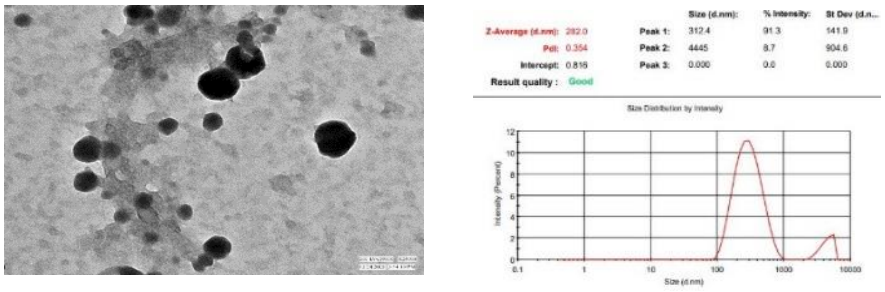


*Fig 3. TEM image and particle size of optimized invasomes*

**Objective II:** ***To study the penetration enhancing effect of different terpenes present in the invasomes***

*Ex vivo* skin permeation studies were performed using pig ear skin for 24 hours. The cumulative permeation of the formulated curcumin invasomes ranged from 3589.00±1.70 to 4335.11± 1.19 μg/cm$^2$. The invasomal formulation made with citral (0.5%,1%and 1.5%) showed a maximum cumulative curcumin permeation of 3891.50 ±2.00, 4175.80 ± 2.22 and 4335.11± 1.19 μg/cm2 after 24 hours whereas the drug solution had a cumulative permeation of 1621.50 ± 1.22 μg/cm$^2$ (*Fig 4*). With a rise in terpene content, a greater quantity of curcumin permeated across the porcine skin. *Ex vivo* permeation results suggest smaller size of the invasomes containing citral facilitated better permeation across the stratum corneum barrier of the pig skin

by disrupting highly ordered intercellular packing of the stratum corneum lipids and increasing drug diffusivity. Skin retention study ascertains the amount of curcumin that retained in the pig ear skin after the *ex vivo* permeation study.

The value of permeation flux ranged from 157.5±0.234 to 188.33±0.33 µg/cm$^2$/h for curcumin invasomes whereas curcumin solution had a permeation flux of 71.43±0.05 µg/cm$^2$/h. Invasomes containing 1.5% citral showed 2.63 times increase in the permeation flux when compared with curcumin solution and formulations containing other terpenes (*Fig 5*). Curcumin solution had a permeability coefficient of 7.1×10$^{-3}$ cm/h whereas the permeability coefficient of invasomal formulation was found to be 15.8×10$^{-3}$ to 18.8×10$^{-3}$ cm/h. All the prepared invasomal formulations showed a higher permeation flux and permeability coefficient when compared to the curcumin solution. The amount of curcumin that retained in the pig ear skin ranged from 580.26±0.50 to 914.36±0.26 µg/cm$^2$. Invasomal formulation C3 demonstrated the highest drug retention of 914.36±0.26 µg/cm$^2$ when compared to the curcumin solution which was 308.43±0.12 µg/cm$^2$.

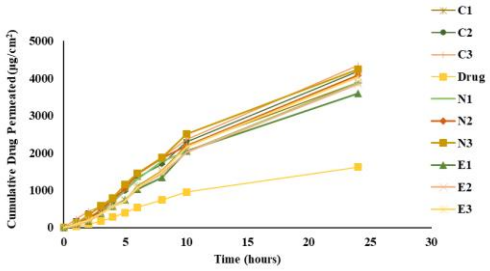


*Fig 4. Ex vivo permeation study*

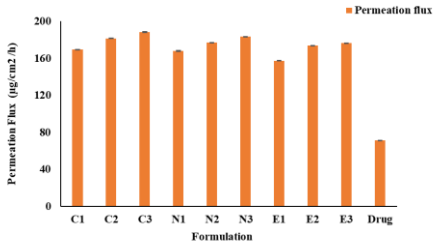


*Fig 5. Permeation Flux of invasomal formulations*

The amount of curcumin retained in the skin increased with an increase in concentration of terpene which is attributed to increased size of invasomal vesicle.

Literature suggests that monoterpenes with aldehyde group in their structure are better sorption promoters than cyclic monoterpenes with oxide group (eucalyptol) or sesquiterpenes with an alcohol group (nerolidol). Invasomes containing citral demonstrated the smallest particle size with maximum drug entrapment efficiency which may be the reason for the higher *ex vivo* permeation in comparison to invasomes

incorporating nerolidol and eucalyptol. Factors like log P value, molecular weight, chemical structure and lipophilicity of drug play a crucial role in determining the penetration enhancing effect of the terpenes present in invasomes. Citral was found to be a better penetration enhancer in the curcumin invasomal formulation which is evident by the permeation flux and permeability coefficients.

**Objective III:** ***Formulation and evaluation of topical invasomal gel of curcumin for effective management of plaque psoriasis***

**Evaluation of Gel:** The invasomal gel appeared yellow-orange in colour, which was easily washable and was free from the presence of any gritty particle with a good homogeneity. The gel formulation had a pH of 5.8 ± 0.07, which was within the skin's physiological pH range and hence the developed gel is safe, non-irritating and suitable for topical administration. The prepared gel demonstrated an occlusive nature which augments the permeation of active drug, thereby enhancing the efficacy.

The spreadability of the gel formulation was determined, by measuring the area of 0.5 g gel placed between two horizontal plates (20×20 $cm^2$) after 1 minute when 125 g of weight was placed above the plates. The area of gel increased **4.5 times** when 125 g weight was added to the plates, which suggest good spreadability of the gel.

| | **Diameter (cm)** | **Area ($cm^2$)** |
|---|---|---|
| Before (adding weight) | 1.6 cm | 2.00 |
| After (adding weight) | 3.4 cm | 9.07 |

*Table 1.Spreadability of gel*

Extrudability was evaluated in terms of weight which can produce a ribbon of 0.5 cm in 10 seconds when the gel was filled in collapsible tubes. The developed invasomal gel showed an extrudability of 5.73 ± 1.05 g, which suggest that the gel is having good extrudability with a viscosity of 97800 cp at 20 rpm**.**

During the *in vitro* studies, the cumulative amount of curcumin released after 24 hours from the invasomal gel was much higher when compared to plain curcumin gel (*Fig 6*). *Ex vivo* permeation studies suggested that the cumulative amount of curcumin that permeated the porcine skin, flux and permeability coefficient were higher than the plain curcumin gel (*Fig 7*).

| | ***In-Vitro* Release Study** | ***Ex-vivo* Permeation study** | **Skin Retention Study** | | | |
|---|---|---|---|---|---|---|
| Formulation | Cumulative Drug Release after 24 hours (µg/cm$^2$) | Cumulative Drug Permeated after 24 hours (µg/cm$^2$) | Permeation flux (J, µg/cm$^2$ /h) | Enhancement Ration (ER) | Amount deposited (µg/cm$^2$) | Permeability coefficient |
| Invasomal Gel | 4696.25±51.52 | 4219.74 ± 48.60 | 186.6 ±0.26 | 3.03 | 712.76±2.09 | 18.6 ×10-3 |
| Plain Gel | 1791.77±25.18 | 1376.69 ± 5.8 | 61.60 ±0.23 | 1.00 | 339.62±1.24 | $6.2\times10^{-3}$ |

*Table 2. Results for In vitro release, Ex vivo permeation and skin retention study*

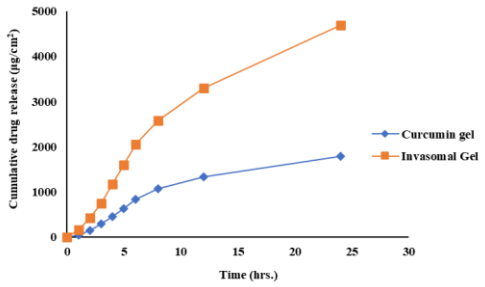


*Fig 6. Cumulative drug release (µg/cm$^2$) from gel*

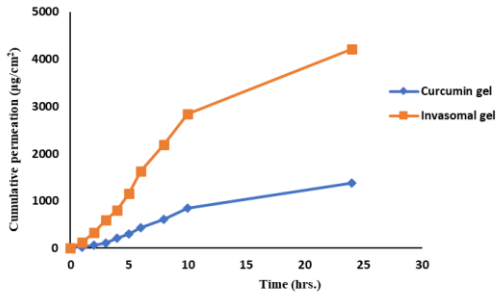


*Fig 7. Ex vivo permeation of gel*

The *in vitro* drug release data was analysed using several release kinetics models such as first order, zero order, Higuchi's equation and Korsmeyer Peppas equation. The best model for describing the drug release kinetics of the invasomal gel was found to be the one with the highest correlation ($R^2$) value. According

to the greatest correlation ($R^2$) value, the gel ($R^2$ = 0.984) conformed well to the Higuchi model followed by Korsmeyer–Peppas ($R^2$ = 0.952), first-order ($R^2$ = 0.921) and zero order ($R^2$ = 0.9155) models.

**Stability Study:**

The optimized invasomal formulation was stored at 4 ± 1 °C, 30 ± 1 °C and 45 ± 1 °C under controlled humidity of 75% RH for 1, 2 and 4 months. Physical appearance, entrapment efficiency and vesicle size were used to assess physicochemical stability (*Fig 8*).

| Parameters | Initial | 1 months | | | 2 months | | | 4 months | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Temperature (°C) | | 4±1 | 30±1 | 45±1 | 4±1 | 30 ± 1 | 45±1 | 4±1 | 30±1 | 45± 1 |
| Appearance | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Vesicle Size (nm) | 282.0 | 286.57 | 284.13 | 292.56 | 293.24 | 288.78 | 300.49 | 300.43 | 292.05 | 306.88 |
| % Entrapment | 85.84 | 83.27 | 84.53 | 82.48 | 82.49 | 82.22 | 80.76 | 81.32 | 81.17 | 78.78 |

*Table 3. Stability Study of Optimized Invasomal Formulation*

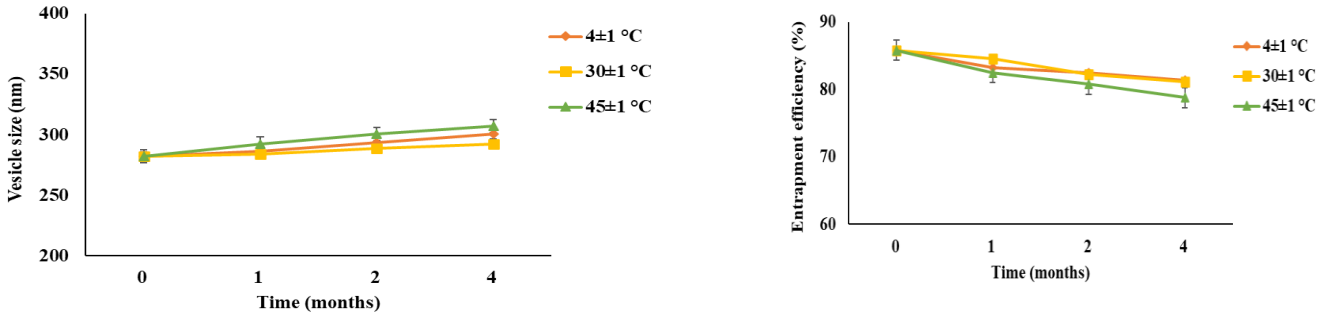


*Fig 8. Stability study of optimized invasomal formulation*

Invasomal gel was kept at 4±2°C and 25±2°C and the gels were analysed for different parameters at specific time intervals of 0, 1, 3 and 6 months

| | | 1 months | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|---|
| Temperature (°C) | Initial | 4±2°C | 25±2°C | 4±2°C | 25±2°C | 4±2°C | 25±2°C |
| Colour | Yellow-Orange | Yellow-Orange | Yellow-Orange | Yellow-Orange | Yellow-Orange | Yellow-Orange | Yellow-Orange |
| Appearance | Smooth | Smooth | Smooth | Smooth | Smooth | Smooth | Smooth |
| Clarity | Clear | Clear | Clear | Clear | Clear | Clear | Clear |
| pH | 5.8 | 5.8 | 5.8 | 5.5 | 5.3 | 5.2 | 5 |
| Homogeneity | *** | *** | *** | *** | * | ** | * |
| Washability | Washable | Washable | Washable | Washable | Washable | Washable | Washable |
| Odour | NO | NO | NO | NO | NO | NO | NO |

*** Excellent ** Good * satisfactory

*Table 4. Stability Study of Invasomal Gel*

***In vivo* Antipsoriatic Activity:**

Imiquimod induced psoriatic model in BALB/c mice was used to test the *in vivo* efficiency of the formulated curcumin invasomal gel, which was compared to plain curcumin gel in terms of therapeutic effectiveness. Psoriasis severity index scores were collected after the applying the formulations which was used for measuring factors like scaling, skin thickness and redness.

Imiquimod cream (Imiquad 5% w/w Glenmark Pharmaceuticals Ltd), 62.5 mg/day was applied topically on the shaved skin of the mice for 10 days to induce psoriasis. After psoriasis induction, the mice were separated into four different groups (n=4). Group I was the disease-free control group, Group II was psoriasis-induced group with no treatment; Group III and group IV were the diseased group which were treated with curcumin gel and curcumin invasomal gel respectively. The therapy was continued for ten days following the onset of psoriasis. Symptoms of psoriasis that is thickness, scaling and redness were graded

as none, mild, moderate, severe, or extremely severe using grades 0, 1, 2, 3, and 4. The anti-psoriatic potentiality of the invasomal gel was determined through the PASI score (Psoriasis Area and Severity Index) as well as skin histology.

All the mice groups demonstrated signs of psoriasis on day 0 of therapy that is increased inflammation, thickness of skin, redness and scaly lesion. At day 4, the mice treated with curcumin invasomal gel showed faster improvement in psoriatic symptoms than the animals treated with curcumin gel. The psoriatic symptoms of the mice treated with invasomal curcumin gel completely subsided by day 10 (*Fig.9*). Curcumin invasomal gel alleviated psoriasis-like symptoms and shortened therapy time, however curcumin gel was shown to be less beneficial and was unable to completely cure psoriasis-like symptoms after a 10-day therapy period. This is due to inadequate curcumin penetration following topical administration in the form of curcumin gel.

Skin redness is attributed to the release of cytokines and other inflammatory molecule which actively leads to vasodilation in the dermis. The scaling in psoriasis is caused by poor differentiation of keratinocytes following enhanced proliferation, as well as abnormal cytokines (IL-1, TNF-). Other metrics, such as skin thickness, show increased keratinocyte proliferation as a result of proinflammatory cytokines (IL-20, IL-22). The skin of the mice developed all three indicators (erythema, scaling and thickness) on the third day of psoriasis induction, which worsened steadily until the eleventh day. Following psoriasis induction, therapy with the prepared curcumin invasomal gel was initiated at the location of psoriatic skin from day 10 to day 20. On the 20th day, mice treated with curcumin invasomal gel exhibited a considerable reduction in redness compared to mice treated with curcumin gel, and there was no evidence of redness

After 10 days of topical treatment of invasomal gel, the scaling indications vanished totally. Skin thickness symptoms were reduced in animals treated with invasomal gel on the fifth day of therapy. The group treated with curcumin gel showed no significant reduction in skin thickness until the completion of therapy (Fig.4)

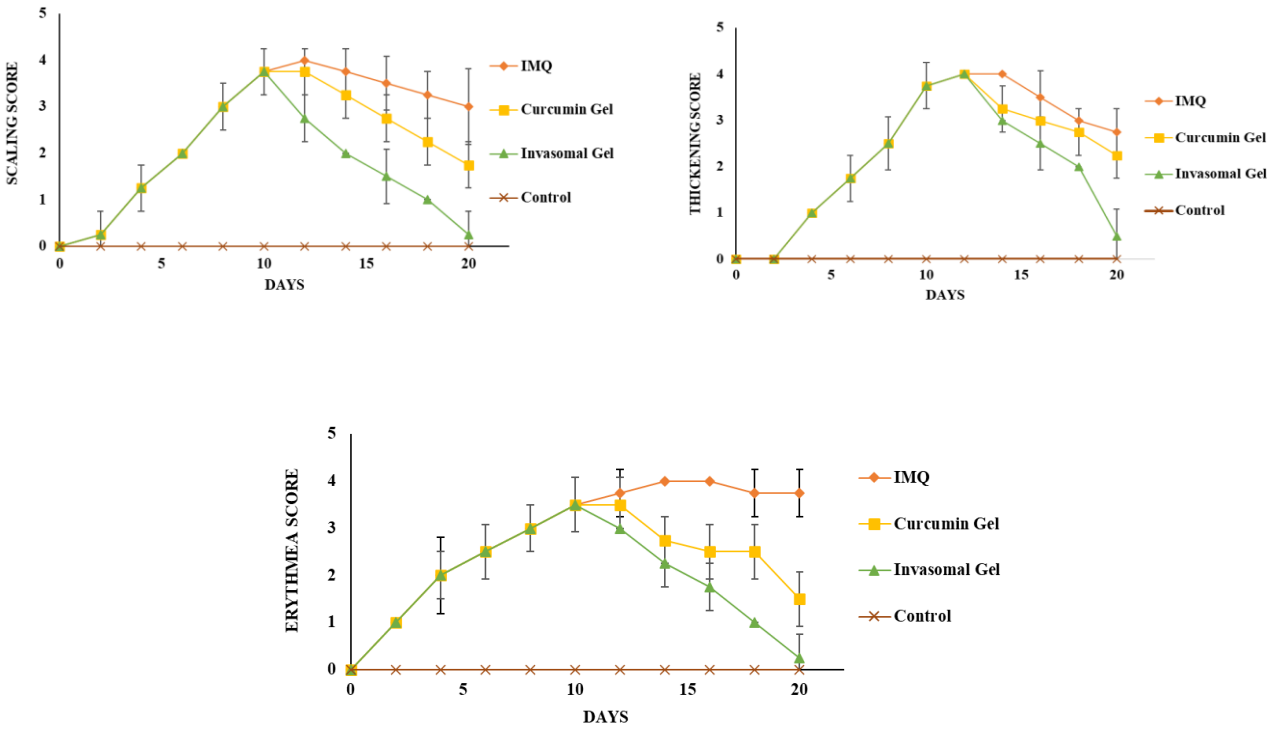


*Fig 9.Comparison of Psoriasis severity index for plain and Invasomal gel (Mean ± SD).*

Higher efficiency of curcumin invasomal gel is due to the augmented permeation of curcumin in psoriasis affected skin. The activity of phosphorylase kinase in skin of psoriatic patients is found to be considerably higher. The increased activity of the enzyme results in an increase in release of inflammatory mediators. When curcumin invasomal gel is applied topically, curcumin loaded invasomes transfer curcumin into the deeper skin layer or the bloodstream where curcumin inhibits the activity phosphorylase kinase resulting in increased antipsoriatic activity.

**Histopathology of Skin:**

Intact epidermis and viable dermis were obtained in the case of group I. Psoriatic skin showed the episodes of keratosis, hyperkeratosis, parakeratosis and some signs of orthokeratosis. Excessive hyperkeratosis and

parakeratosis was observed in group II suggesting the induction of disease. Curcumin invasomal gel treated group displayed normal skin with very mild keratosis probably due to better penetration and retention with slow release of curcumin on skin (*Fig 10*).

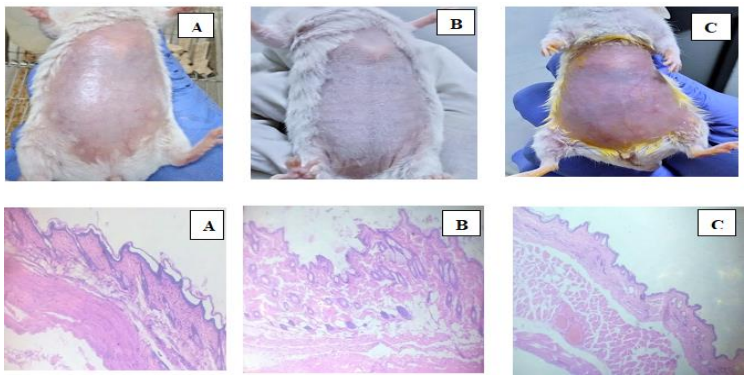


*Fig 10. Histopathology of mice skin samples A)Healthy Skin B)Psoriatic skin C)Invasomal Gel treated skin*

**6. Conclusion:**

The research investigated the efficiency of invasomal vesicles as a suitable carrier for administering curcumin via the transdermal route for effective management of plaque psoriasis. Using a mechanical dispersion approach, nano invasomal vesicles containing curcumin were created, and the resulting formulations were evaluated and optimised on the basis of vesicle size, percentage entrapment, *ex vivo* permeation and *in vitro* drug release using a factorial design. Invasomal formulation containing citral in 1.5% concentration showed the maximum percentage entrapment, cumulative release and permeation. Transmission electron microscope revealed spherical-shape of the invasomal vesicles.

Topical gel of optimised formulation was prepared by mixing with Carbopol 934 base, and a yellow-orange gel with a pH of 5.8 ± 0.07 was obtained, demonstrating high extrudability, spreadability, and uniformity. *In vitro* study affirmed that the invasomal gel adhered well to the Higuchi model with a cumulative release of 4696.25±51.52 µg/cm$^2$. The invasomal gel had a permeation flux three times more than that of plain gel with a cumulative permeation of 4219.74 ± 48.60 µg/cm$^2$. Invasomal gel was able to attain a higher flux and maximum skin retention when compared to plain curcumin gel which is due to the presence of citral

and ethanol in the vesicle which act synergistically by disturbing the lipids of stratum corneum, collaborating with the intercellular proteins molecules and intensifying the partioning of curcumin into the skin layer.

Imiquimod induced psoriatic model was used to test the *in vivo* efficiency of the formulated curcumin invasomal gel. Curcumin invasomal gel was compared to plain curcumin gel in terms of therapeutic effectiveness. The psoriatic symptoms of the mice treated with invasomal curcumin gel completely subsided by day 10 whereas plain curcumin gel was unable to completely cure psoriasis-like symptoms after a 10-day therapy period. This is due to inadequate curcumin penetration following topical administration in the form of curcumin gel. Higher efficiency of curcumin invasomal gel is due to the augmented permeation of curcumin in psoriasis affected skin which is attributed to the ethanol and citral present in the invasomal composition which provide greater fluidity, permeability and deformability.

**7. List of Publications/Presentations/Posters:**

**Publications:**


1. **Kumar B**, Pandey M, Aggarwal R, Sahoo P.K. A comprehensive review on invasomal carriers incorporating natural terpenes for augmented transdermal delivery. Future journal of Pharmaceutical Sciences.2022; 8(50)
2. **Kumar B**, Sahoo P.K, Manchanda S. Formulation, characterization and *ex vivo* study of curcumin nano-invasomal gel for enhanced transdermal delivery. Open Nano. 2022; 7
3. **Kumar B**, Sahoo P.K, Manchanda S. Development of eucalyptol enriched nano vesicles for better transdermal delivery of curcumin: Preparation, characterisation and *ex vivo* skin analysis. Nanomedicine Journal. 2022; 9(3); 223-230.
4. **Kumar B**, Aggarwal R, Targhotra M, Sahoo P.K. Novel Topical Drug Delivery Approaches for the Management of Psoriasis. International Journal of Pharmaceutical Sciences and Nanotechnology. September-October 2020: 13(5). DOI: 10.37285/ijpsn.2020.13.5.2

**Presentations/Posters:**

1. E-poster presentation in international conference on Emerging Biomaterials for advanced applications (ICEBAA 2022)
2. **First prize** in e-poster presentation in international conference on Advances in Pharmaceutical and Health Sciences held a KIET school of Pharmacy.

**8. References:**


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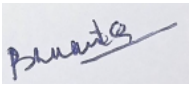

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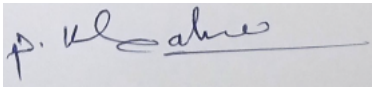

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